REMARKS

ON

METHODS OF INCREASING AND DIMINISHING THE COAGULABILITY OF THE BLOOD,

WITH ESPECIAL
REFERENCE TO THEIR THERAPEUTIC EMPLOYMENT.

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We may begin by the consideration of the methods by which blood coagulability can be increased, since these methods form the basis of the rational therapeutics of hæmophilia and of the treatment of all cases of hæmorrhage and aneurysm which are not accessible to surgical treatment. I have already in the British Medical Journal[1] indicated one of these methods, which consists in the addition of lime salts to the blood, and I now propose to call attention to a further method of increasing coagulability which consists in increasing—by inhalation of the gas or otherwise—the amount of carbonic acid in the blood. It will be convenient to summarise in the form of a series of propositions the results which have been obtained by the experimental application of these methods.

The Addition of Calcium Chloride to Extravascular Blood causes it to coagulate more rapidly.

I have already established this in previous communications,[2] and I have suggested[3] that this fact may be turned to practical account by employing weak (that is 0.25-0.5 per cent.) solutions of calcium chloride as "physiological styptics." I have further pointed out[4] that the efficacy of these styptics may be increased by combining the calcium chloride with solutions of cell nucleo-albumens, that is, with albuminous substances which can be obtained from the aqueous extracts of any cellular tissues—for example, thymus, thyroid, testicle, gastric and other mucous membranes. The practical utility of such physiological

styptics remains a matter for clinical experiment by others; but I desire to point out that the efficacy of any particular sample of styptic can now be readily put to the test before it is employed clinically by taking advantage of the coagulation tubes with mixing chambers which I have recently described and figured in this JOURNAL.[5] The following examples will suffice to indicate the amount of acceleration that may be expected:

Blood drawn from finger of G. C. (a hæmophiliac boy).—Coagulation time of unmixed blood 45 minutes. Coagulation time of blood which had received an addition of $\frac{1}{8}$ vol. of a 1 per cent. calcium chloride solution 9½ minutes. (Experiment conducted at temperature of air, *circ.* 57° F.)

Blood drawn from finger of the same boy one fortnight later.—Coagulation time of unmixed blood exceeds 45 minutes. Coagulation time of the same blood after receiving an addition of $\frac{1}{8}$th of a 1 per cent. calcium chloride solution less than 19 minutes. (Experiment conducted at temperature of air, *circ.* 42° F.)

Blood drawn from the finger of a woman (Mrs. H.) who had handed down the hæmorrhagic diathesis to two sons.—Coagulation time of unmixed blood 5 minutes 25 seconds. Coagulation time of blood after receiving an addition of $\frac{1}{8}$ vol. of a 1 per cent. calcium chloride solution 2 minutes 45 seconds. (Experiment conducted at 18.5° C.)

My own blood, June 3rd, 1894.—Coagulation time of unmixed blood 5 minutes. Coagulation time after addition of $\frac{1}{3}$ vol. of a solution of nucleo-albumen combined with 1 per cent. calcium chloride 2 minutes 30 seconds. (Experiment conducted at temperature of 18.5° C.)

My own blood, June 22nd, 1894.—Coagulation time of unmixed blood 5 minutes 45 seconds. Coagulation time after addition of $\frac{1}{3}$ vol. of the same styptic 2 minutes. (Experiment conducted at 18.5° C.)

It will be observed from the above examples that the addition of a "physiological styptic" may give us a very rapid coagulation. By its very nature, however, it cannot give us the instantaneous cessation of bleeding which we can obtain, if we care to pay the price for it, with an ordinary escharotic styptic.

THE INTERNAL ADMINISTRATION OF CALCIUM CHLORIDE INCREASES THE COAGULABILITY OF THE BLOOD.

I have already in a previous paper shown this to be the case (*a*) in the blood of animals (dogs and rabbits), (*b*) in the blood of my friend Dr. Leonard Rogers and in my own blood; and (*c*) in the case of a hæmophiliac boy who was under my care in July, 1893. I need not do more than supplement this by the following observations on certain families of hæmophiliacs:

CASE I. *Hæmophilia Inherited from Mother and Grandmother.*—This reported derivation of the disease was confirmed by the fact (*a*) that the mother's blood had a coagulation time of 7 minutes, as compared with a coagulation time of 3 minutes in the father's blood (both under identical conditions of temperature and diet), and (*b*), by the fact that the grandmother's blood had a coagulation time of 11 minutes as compared with a coagulation time of 5¼ minutes in the grandfather's blood (both under identical conditions of diet and temperature).

The effect of an administration of calcium chloride to a selected number of the members of this family was as follows :—

Relationship to the Hæmophiliac Boy.	Age.	Coagulation Time before Commencement of Treatment.	Temperature at which the Determination was Made.	Date or Dates on which Calcium Chloride was Administered.	Dose of Calcium Chloride and Number of Daily Doses.	Coagulation Time after Treatment.	Temperature at which the Determination was Made.
		Min. Sec.	F.		Grammes.	Min. Sec.	F.
Maternal grandmother	68	11	55°	2-11-93	0.6 b.i.d.	5	57°
		5	57°	3-11-93	0.6 ,,	6 30	52°
Mother ...	28	6 45	55°	2-11-93	0.6 ,,	4 35	57°
		4 35	57°	3-11-93	0.6 ,,	3 25	52°
Eldest sister	9½	11 45	55°	2-11-93	0.3 ,,	9	57°
		9	57°	3-11-93	0.3 ,,	10	52°
Fifth sister ...	1½	12 20	55°	2-11-93	0.3 ,,	10 15	57°
		10 15	57°	3-11-93	0.3 ,,	7 20	52°
Hæmophiliac boy himself...	3	23 (?)	55°	2-11-93	0.3 ,,	35 (?)	57°
		35 (?)	57°	3-11-93	0.6 ,,	21 (?)	52°
		21 (?)	52°	4-7-11-93	0.3 ,,	29 (?)	41°
		29 (?)	41°	13-15-11-93	0.7 ,,	45 (?)	42.5°
Maternal first cousin (boy)	11	8 20	55°	2-11-93	0.6 ,,	4 30	57°

It will be noticed that evidence was obtained of increased coagulability of all the members of the family except the hæmophiliac boy himself. It is impossible to be certain whether in his case there was any increase of coagulability or not for the determinations of coagulability were made at such unfavourable temperatures that it was a matter of difficulty to obtain a correct measure of his coagulability.

I am indebted to Sir William Jenner, Bart., for the opportunity of studying, and for much help in the study, of these cases.

Case II.—Hæmophilia said to be inherited through the mother. No confirmation of this history obtained on comparing the mother's coagulation time (3½ minutes at 18.5° C.) with the father's coagulation time (3 minutes 40 seconds, at 18.5° C.).

Patient.	Age.	Coagulation Time before Treatment.	Date on which $CaCl_2$ was Administered.	Dose and Number of Daily Doses.	Coagulation Time after Treatment.	Temperature at which Determinations were Made.
Hæmophiliac boy ...	9	Over 60 min.	14-4-94	2 grammes b. i. d.	27 min.	18.5° C.
		27 min.	15-4-94	2 grammes b. i. d.	13 min.	18.5° C.
Hæmophiliac boy ...	7	6 min. 40 sec.	14-4-94	2 grammes b. i. d.	4 min.	18.5° C.

It will be seen that the administration of comparatively

large doses of lime was successful in reducing coagulation time in both these cases.

CASE III.—Hæmophilia of very moderate degree.

Patient.	Age.	Coagulation Time before Treatment.	Date on which $CaCl_2$ was Administered.	Dose and Number of Daily Doses.	Coagulation Time after Treatment.	Temperature at which Determinations were Made.
Male ...	30 *circ*	7 min. 30 sec.	22-3-94	2 grammes b. i. d.	5 min. 50 sec.	18.5° C.

I am indebted to my friend Mr. N. Ridley for the opportunity of studying these cases.

It has thus been shown in the case of four quite unrelated hæmophiliac families (that is, in the cases just reported and in the case reported in my previous paper[6]) that the administration of calcium chloride causes an increase of blood coagulability. I have collected some, but as yet insufficient, evidence of the same favourable effect in the case of three other hæmophiliac families which have come under my observation. I have also notes of a case in which the administration of calcium chloride enabled an operation for nasal polypi to be successfully carried out. An operation had been attempted on a previous occasion upon the patient in question (a girl who is a member of one of the families of hæmophiliacs last referred to), but it was apparently found necessary to abandon it owing to the onset of serious hæmorrhage. A brother of this girl died from hæmorrhage after extraction of a tooth, and his case has been reported in the Army Medical Reports for 1893 by Surgeon-Captain Grenville E. Moffett. I am indebted to this officer for an opportunity of studying this hæmophiliac family.

INTERNAL ADMINISTRATION OF CALCIUM CHLORIDE OFTEN CAUSES AN ARREST OF HÆMORRHAGE.

The proof that internal administration of calcium chloride frequently brings about an arrest of hæmorrhage is a much easier matter than the proof of the occurrence of increased blood coagulability after the administration of lime. This is evident when we consider that an arrest of hæmorrhage obtrudes itself upon observation, whereas an increase of blood coagulability may occur and may pass unperceived, unless we are fortunate enough to hit off the proper time for making our examination of the blood. In actual experience I have on several occasions failed to obtain a record of increased coagulability in cases where there could hardly be any doubt that the arrest of hæmorrhage which had taken place was attributable to the administration of the calcium chloride.

Instances of arrest of hæmorrhage (hæmoptysis, frequently recurring epistaxis) after the administration of lime salts have been put on record by me in my previous paper.[7] Since the date of that paper I have seen other and equally successful results from this treatment, especially in hæmophiliac menorrhagia. Mr. Mayo Robson has also put similar cases on record—arrest of bleeding in surgical operations on the

liver and in menorrhagia. A much greater evidential value, however, attaches to cases of arrest of actual hæmophiliac hæmorrhage, for in these we have an opportunity of contrasting hæmorrhages which were left untreated with hæmorrhages in the same patients which have been treated with calcium chloride. It will suffice to say that I have learned from four different sources—in three instances from the medical men in charge—of the successful arrest of hæmophiliac hæmorrhage under the influence of calcium chloride. The details of a fifth case, which was successfully treated by the inhalation of carbonic acid combined with the internal administration of lime salts, will be given in another part of this paper.

The Continued Administration of Large Doses of Calcium Chloride is not Effectual in Keeping up a Permanent Condition of Increased Blood Coagulability.

I have already pointed out this fact in connection with the case of hæmophilia recorded in my previous [8] paper. In the case in point, the administration of calcium chloride (1 gramme t. i. d.) reduced the coagulation time of the blood from 10 minutes to 5 minutes, but on the third day of the treatment, which was also the last day of the experiment, coagulation time was diminished beyond all previous record. The same phenomenon manifested itself in the case of my own blood, and precisely similar results are, as I have pointed out, obtained when calcium chloride is added in excessive quantities to extravascular blood. Since the date of the paper just referred to I have repeatedly come across the same phenomenon. I may instance the case of a patient with abdominal aneurysm,[9] for it is especially in cases of aneurysm that a condition of long-continued high blood coagulability is desiderated. I do not propose to go into detail upon this matter here, for the problem of the treatment of aneurysm involves the subordinate problems of the influence of diet and of abstinence from foods and drink and from exercise upon the condition of blood coagulability. I need hardly point out that the study of these problems has not even been seriously commenced, and that there is therefore as yet no scientific justification for the processes of semi-starvation and drugging with iodide of potassium which have been adopted as the routine treatment for aortic aneurysm. If I might judge of the effects of a very spare diet from observations on myself and on the patient in question, I should conclude that such a diet considerably diminishes the coagulability of the blood. For instance, in the case of my own blood, I find that coagulation takes place more slowly than normally when a comparatively long period of inanition (for example, 10 hours) is allowed to intervene between breakfast and dinner. Under such conditions, I have observed my blood to remain fluid for 6 minutes.[10] Three hours after dinner on the occasion in point my coagulation time stood at 2 minutes. I have made several experiments with very similar results. On the other hand Vierordt [11] found that his coagulability was decreased after meals, but I gather that he took beer[12] at dinner, and surmise that he took beer also at his evening meal.

Reverting however to the question of the effect of a continued administration of large doses of lime salts to the

aneurysm patient in question, I found that under the influence of doses of 4 grammes of calcium chloride administered twice daily, the patient's coagulation time decreased from his normal of 6 minutes to a minimum of 4 minutes on the third day of the treatment. On the fourth day coagulability became subnormal, and it reverted to its original level when the administration of calcium chloride was stopped. Similar results were obtained with a morning and evening dose of 3 grammes of calcium chloride. Under the influence of these doses coagulability was increased till a coagulation time of $3\frac{1}{2}$ minutes came under observation on the fourth day of the treatment. On the next day coagulability again began to decline, and coagulation time stood at $6\frac{3}{4}$ minutes on the seventh day of the treatment.

The administration of the lime salt was then again suspended and coagulability increased (this was probably attributable to the elimination of an excess of lime) until the previous maximum coagulability ($3\frac{1}{2}$ minutes) was reached 24 hours after the administration of the lime had been suspended. After this coagulability reverted to its original level, and coagulation times ranging between $6\frac{1}{4}$ minutes and 8 minutes were recorded in the morning and evening determinations of the next two days. The administration of calcium chloride was now begun again (this time 2 grammes of the salt were administered thrice daily), and eight hours after the administration of the first dose, coagulation time stood at $3\frac{1}{2}$ minutes, and under the influence of this treatment, combined with a more generous diet, coagulability increased gradually but irregularly (for there was a temporary fall caused by changes in diet), till on the 12th, 13th, 14th, 15th, and 16th days of this treatment coagulation times of $4\frac{1}{4}$, $4\frac{1}{4}$, $3\frac{1}{4}$, $2\frac{1}{4}$, and $1\frac{1}{2}$ minutes were registered. On the next day after this, though the treatment remained unaltered, coagulability again began to decline, and a few days afterwards the patient passed from under my observation.

Inhalation of Carbonic Acid Gas Increases the Coagulability of the Blood.

After establishing[13] the fact of the increase of blood coagulability under the influence of carbonic acid by direct observations on the condition of blood coagulability in animals (dogs and rabbits) which were supplied in an alternating manner with ordinary atmospheric air and with atmosphere in which the total nitrogen had been replaced by carbonic acid, and after having verified that the inhalation of carbonic acid had a similar effect on my own blood and also upon the blood of some children belonging to a hæmophiliac family under my care, I determined to employ the inhalation of the gas as a therapeutic measure in a case of almost desperate hæmorrhage which occurred in the hæmophiliac boy who was referred to me for study by Sir William Jenner.

The history of the case is as follows: The hæmophiliac heredity can be traced back through three generations of maternal ancestors. The child is at present nearly 4 years old, and has suffered from an almost continuous succession of subcutaneous hæmatomata. In September, 1893, hæmorrhage set in as a result of a fall upon the forehead, which left a scar which was visible for months after. The hæmorrhage was treated by ordinary palliative measures, and finally ceased after lasting some six weeks. The blood is said to

have shown no tendency whatever to clot, unless when the wound had been tightly bandaged up for several days at a time. The coagulation time of this child (taken at temperatures ranging between 42° and 57° F.) oscillated between 45 minutes and 1 hour. On February 2nd, 1894, the child had another fall against a chair, and hurt the frænum of his upper lip, and bled a little at the time. Hæmorrhage came on profusely at night, and his pillow was soaked with blood and a great deal of blood was swallowed. When this was discovered the parents, according to directions previously left with them, administered 0.6 gramme of calcium chloride, and they state[14] that the blood, which had previously shown no sign whatever of clotting, began to clot firmly in two or three hours after the administration of the lime. Bleeding recurred the next day, and in the evening, after the child had fallen asleep, his mouth was found quite filled with blood clot. On February 4th, 5th, and 6th, bleeding recurred at intervals (probably owing to the frequent dislodgment of the clot). Calcium chloride had been administered all this time in 0.6 gramme doses twice daily. The child was seen by me on February 6th, and I found a scratch about one-eighth of an inch long, covered over by coagulated blood on the frænum of the upper lip. There was no oozing from the wound. A drop of blood was drawn off from the child's finger, and coagulation time (determined at 37° C.) was found to be 2 minutes 25 seconds,[15] and the addition of lime to the extravascular blood was found not to effect any acceleration of coagulation time.[16] The calcium chloride appears, therefore, to have done all that could have been expected of it, and yet there had been frequent recurrences of the hæmorrhage when the clot became dislodged. In view of these facts I determined to administer carbonic acid gas with a view to still further increasing blood coagulability. I hoped in this way to cause the blood to clot, not only on the surface of the wound, but also some distance up the lumina of the ruptured vessels. Guided by these considerations I inserted a soft india-rubber tube into the child's mouth, and connected it up with a Kipp's gas apparatus, which I had brought with me. I determined the coagulation time of the child's blood while the carbonic acid was being administered to him, and found that it was accelerated to 1 minute 40 seconds (determined at 37° C.).

The child was not seen by me again till February 12th, when I received another urgent summons saying that the hæmorrhage, which had ceased for 24 hours after the inhalation of the carbonic acid, had broken out afresh, and had continued ever since. Calcium chloride had been administered twice daily in 0.6 gramme doses from the 7th to the 11th, when the child vomited and refused to take it. On arrival I found the child absolutely blanched and tetchy to a painful degree. Determinations of coagulability were therefore out of the question. Blood was found to be oozing from the frænum of the upper lip, and there was a trace, but only a trace, of clot around the wound. Carbonic acid was immediately administered in the same manner as before, and under its influence bleeding broke out copiously. When, however, the child came more under the influence of the gas, and his struggles ceased, the blood clotted instantaneously, so that even the film of blood which was drawn out between the upper and the lower lip when the mouth was opened in-

stantly congealed into a clot. I proceeded to remove the large clot of blood which had formed round the gum, and found it to be of extraordinary firm texture. A small clot instantly reformed round the cut, and the hæmorrhage ceased and the child fell asleep. The administration of the gas was continued for half an hour. The gasogene was then recharged and was left under the parents' charge. Hæmorrhage broke out afresh twice or three times in the course of the night, when the clots became dislodged, but clotting is reported to have taken place as soon as the inhalation of the gas was renewed. After this there was no further return of hæmorrhage, and convalescence took place.

In view of the apparently favourable results which have just been recorded, I resorted to inhalations of carbonic acid as a therapeutic measure in the case of abdominal aneurysm which I have already referred to. The method of administration which was finally selected as the most suitable consisted in filling an india-rubber bag (a water bed was pressed into this service) with carbonic acid gas, and in connecting up this bag with the mouthpiece of a Clover's inhaler. This arrangement allowed of the admixture of any desired amount of air with the gas as it escaped from the india-rubber bag. The administration of the gas was superadded to the medicinal treatment which was adopted. The results of these inhalations on blood coagulability are recorded in the following table:

Date.	Coagulation Time of Patient while Breathing Ordinary Air.	Coagulation Time of Patient a Few Minutes Later when Breathing a Mixture of CO_2 and Air.
	Min. Sec.	Min. Sec.
May 1, 1894	6 0	5 0
,, 3, ,, ...	6 45	5 0
,, 4, ,, ...	5 35	4 25
,, 5, ,, ...	4 7	3 18
,, 6, ,, ...	5 0	3 45
,, 8, ,, ...	7 45	6 15
,, 13, ,, ...	4 5	2 30
,, 15, ,, ...	3 30	3 15
,, 16, ,, ...	5 10	3 15
,, 17, ,, ...	9 40	5 47
,, 18, ,, ...	7 0	5 40
,, 19, ,, ...	4 25	3 15
,, 20, ,, ...	5 0	3 45
,, 21, ,, ...	4 52	2 42
,, 22, ,, ...	5 0	2 50
,, 23, ,, ...	4 20	3 0
,, 24, ,, ...	4 30	2 23
,, 25, ,, ...	3 22	1 55
,, 28, ,, ...	2 37	2 15
,, 30, ,, ...	3 52	3 20
,, 31, ,, ...	4 15	3 30
June 2, ,, ...	10 0	4 30

It is thus evident that a very appreciable increase of coagulability can be obtained by the inhalation of carbonic acid. The following facts are to be noted with respect to the manner of administration: (*a*) It is essential to give a sufficiency of oxygen or of ordinary air with the carbonic acid, not only because a neglect of this precaution causes extreme dyspnœa, but also because an anoxyhæmic condition of the blood appears to induce a condition of diminished

blood coagulability. (*b*) Intravascular thrombosis may occur when carbonic acid is administered to an animal whose blood coagulability is abnormally high. I have, for instance, seen it supervene under these circumstances in animals whose blood coagulability had already been increased by the administration of calcium chloride. Naturally, therefore, the administration of carbonic acid was omitted in the case of the aneurysm patient in question on the days in which a coagulation time of less than $2\frac{1}{2}$ minutes was registered. In this connection I may advert to the fact that Sir Joseph Fayrer has pointed out[17] that in persons whose blood is abnormally coagulable intravascular thrombosis tends to occur (*a*) after any violent muscular exertion, (*b*) as a sequela of surgical operations. It is possible that an accumulation of carbonic acid in the blood is a determining factor in both these cases.

Having thus discussed at some length the methods by which blood coagulability can be increased, we may now take a brief survey of the *methods by which blood coagulability can be diminished.* The physiologist is familiar with some half-dozen methods by which the coagulation of the blood may be indefinitely postponed. Some of these methods—for instance, the addition of neutral salts to the blood or the cooling of the blood to a temperature approaching the freezing point—are not applicable to the intravascular blood. Again, other methods—for example, the addition of peptone or leech extract[18] to the blood—are therapeutically impracticable, because these substances fail of their effect when they are administered by the stomach, and because their injection into the veins is either dangerous or undesirable. In short, of the methods that are familiar to the physiologist, one method alone promises to be of service to the therapeutist. This method consists in operating upon the lime salts of the blood in such a manner as to render a certain portion of these salts unavailable for purposes of coagulation. Either oxalic, citric, tartaric, or malic acids, or the soluble salts of these acids, are at our disposal for this purpose. Oxalic acid and oxalates are, however, contra-indicated owing to their poisonous properties. I therefore experimented upon animals and upon myself with tartrates and citrates, taking them by the stomach. I was, however, unsuccessful in obtaining a diminution of coagulability by this method, either in animals or in myself, though I both administered and took large doses of the salts (half an ounce and upwards).

Citric Acid Diminishes Blood Coagulability.

I then experimented with tartaric and with citric acids, and have by this method obtained a diminished coagulability in all my experiments. The protocols of some of these experiments are subjoined:

Dog 1 (*circ.* 6 kilos. weight): 12.35 P.M., coagulation time 1 min. 50 sec.; 12.55 P.M., 15 grammes of tartaric acid administered by mouth; 1.5 P.M., dog vomits; 3 P.M., 15 grammes of citric acid administered by mouth; 3.45 P.M., coagulation time 3 min. 45 sec.

Next day at 12.45 P.M., coagulation time 2 min. 55 sec.; 1.30 P.M., 1 gramme citric acid administered hypodermically in 20 c.c. of distilled water; 2.30 P.M., coagulation time 3 min. 50 sec.; 4 P.M., coagulation time 4 min. 55 sec.; bleeds very freely from puncture in the ear.

Dog 2 (*circ.* 6 kilos. weight): 1.30 P.M., coagulation time 1 min. 30 sec.; 1.35 P.M., 1 gramme of citric acid hypodermically in 20 c.c. of water; 2.45 P.M., coagulation time 3 min. 8 P.M., coagulation time 3 min. 30 sec.

Next day at 11.35 A.M., coagulation time 1 min. 35 sec.; 11.40 A.M., 2 grammes of citric acid hypodermically in 40 c.c. of water; 1.20 P.M., coagulation time 2 min. 10 sec.; 4.30 P.M., coagulation time 3 min. 30 sec.

Dog 3 (*circ.* 7 kilos. weight): 12 noon, coagulation time 1 min. 50 sec.; 12.5 P.M., 2 grammes of citric acid hypodermically in 40 c.c. of water; 1.50 P.M., coagulation time 2 min. 30 sec.; 4 P.M., coagulation time 1 min. 50 sec.

The injections were apparently painless, and no alteration of respiration was observed.

Experiments on myself: 1.45 P.M., 4½ hours after a light breakfast, coagulation time 5 min.; 4.15 P.M., 2¼ hours after a light luncheon, coagulation time 3 min. 10 sec.; 4.30 P.M., 6 grammes of citric acid swallowed in 50 c.c. of water; 6.40 P.M., coagulation time 7 min. 15 sec.; 9.45 P.M., 2 hours after dinner, coagulation time 7 min.; 11.45 P.M., coagulation time less than 3 min. 40 sec.

One week later: 2.30 P.M., one hour after a very light lunch, coagulation time 5 min. 40 sec.; 2.50 P.M., swallowed 5 grammes of citric acid in 100 c.c. of water; 4.50 P.M., coagulation time 6 min. 50 sec.; 5.30 P.M., coagulation time 7 min. 50 sec.; 7 P.M., coagulation time 7 min. 40 sec.; 9.15 P.M., 1¾ hour after dinner, coagulation time 7 min. 30 sec.

The results which are shown upon these last two protocols appear to be conclusive with regard to the only question really at issue, that is, the question whether citric acid can be absorbed from the stomach in sufficient quantities and sufficiently rapidly to exert its influence on coagulation. The evidential value of coagulability determinations which have been recorded is brought out by the fact that, in the very numerous determinations of my own blood coagulability which I have made in the course of the last year, 6 minutes and 15 seconds has been the longest coagulation time which I have registered, and this was at the end of a long fast between breakfast and dinner. I would therefore suggest that we have here a method which may be clinically exploited whenever we find that the coagulability of the blood has become dangerously increased. I need not further particularise the conditions to which the treatment is applicable. I would, however, point out that the effects of the administration ought to be carefully watched, for it is a very easy matter indeed, at any rate when citrates are being injected intravenously, to bind up all the lime salts of the blood in the form of citrates, and thus to render the blood completely uncoagulable and to destroy the irritability of the heart muscle. Before dismissing the subject of the effects of citric acid on the blood, I may be allowed to direct attention to two matters which appear to have a certain clinical importance.

1. The administration of vegetable juices, such as lime juice, which contains citric and other organic acids (*circ.* 8 per cent.), with a certain small admixture (*circ.* 0.3 per cent.) of the soluble salts of these acids, constitutes the routine treatment for scurvy. It is impossible, however, to doubt that this administration of citric acid must be prejudicial in any disorder in which there is a tendency to hæmorrhage, and when there is actual hæmorrhage occurring from the gums even solutions of citrates are contraindicated because of their local action in inhibiting the coagulation of the blood as it issues from the bleeding points. I have, through the kindness of Surgeon-Captain Whitehead, had a recent opportunity of actually observing the unfavourable influence that is exerted on incessant oozing hæmorrhage[19] from the gums by the daily exhibition of the juice of three lemons in the form of cooling drinks. The disadvantages of lemon juice in these cases will be apparent to anyone who will test the effect of

addition of a minimal quantity of lemon juice to a little blood in a capillary tube provided with a mixing chamber. Further, if, as seems assured, scurvy is a condition in which the normal alkalinity of the system has been dangerously diminished, the administration of free citric acid, quite apart from its influence in diminishing blood coagulability, is quite useless for all purposes of treatment, and it is evident that its place ought to be taken by the neutral citrates and tartrates, or preferably acetates, which would supply the alkaline bases which are required by the blood. If solutions of citrates and tartrates are administered in cases where there is hæmorrhage from the gums, the mouth ought evidently to be washed out afterwards with a dilute solution of calcium chloride.

2. The eating of unripe fruits which contain free vegetable acids is known to be a frequent cause of certain urticarious œdemas. These œdemas, and the frequent epistaxis also, if I may judge from my own case and from a few others which I have seen incidentally, are most prone to occur during the period of most active growth—in short, at the period when ossification is proceeding most rapidly, and when lime salts in large quantities are being withdrawn from the blood. It would evidently be interesting, in view of these considerations, to have the condition of blood coagulability tested in these cases.

Having thrown out these suggestions, we may pass on to discuss a further method by which the coagulability of the blood may be intentionally or inadvertently diminished. This method consists in operating upon the gases of the blood with the view of diminishing coagulability by reducing the amount of carbonic acid in the blood. The following methods of diminishing coagulability may probably be subsumed under this heading.

Rapid Respiratory Movements Diminish the Coagulability of the Blood.

This fact was established by Hasebroek[20] upon himself. I have not repeated the observation, but have elsewhere shown that the inhalation of oxygen gas will produce a very appreciable diminution of coagulability in the case of animals. This result is probably due to the very rapid respiratory movements which are induced.

Alcohol Diminishes the Coagulability of the Blood.

Observations upon this subject have been made by Vierordt,[21] and he points out that the probable inference from them is that alcohol diminishes blood coagulability.

The following experiments which I have made seem to establish this fact on a more certain foundation.

My Own Blood (3 to 4 hours after rising, 9 hours after last meal).—4.50 A.M., coagulation time, 6 min.; 5 A.M., ½ pint of champagne; 5.10 A.M., coagulation time, 8 min.; 5.20 A.M., coagulation time, 8 min. 5 sec.; 5.30 A.M., coagulation time, 9 min. 30 sec.

Corporal S.'s Blood (4½ hours after last meal).—0 hour 5 min. P.M., coagulation time, 3 min. 15 sec.; 0 hour 10 min., ½ pint of champagne; 0 hour 30 min., coagulation time, 4 min. 27 sec.; 0 hour 55 min., coagulation time, 4 min. 40 sec.

My Own Blood (4 hours after last meal).—1.20 P.M., coagulation time, 4 min. 15 sec.; 1.30 P.M., 10 c.c. absolute alcohol; 2 P.M., coagulation time, 5 min. 30 sec.; 2.10 P.M., 10 c.c. of absolute alcohol; 2.25 P.M., coagulation time, 6 min. 30 sec.; 2.50 P.M., coagulation time, 5 min. 30 sec.

The effect of alcohol on blood coagulability has evidently a considerable importance in connection with the therapeutics of actual or threatened hæmorrhage.

In conclusion, I have only to emphasise that the methods which have been under discussion are not put forward as adequately-tested therapeutic measures. They may, however, chance to be, if I may so express them unblamed, contributions to the building up of the newer and better system of therapeutics.

NOTES AND REFERENCES.

[1] BRITISH MEDICAL JOURNAL, December 19th, 1891. [2] BRITISH MEDICAL JOURNAL, *loc. cit.* [3] BRITISH MEDICAL JOURNAL, *loc. cit.* [4] *Lancet*, February 25th, 1893. [5] BRITISH MEDICAL JOURNAL, February 3rd, 1894. e obtained from Mr. A. E. Dean, 73, Hatton Garden, EDICAL JOURNAL, July 29th, 1893. [7] BRITISH MEDICAL 1893. [8] *Loc. cit.* [9] This case was very kindly placed these observations by Surgeon Colonel E. Fair- r Cayley. [10] Here and elsewhere in this paper ature at which the determination was made is d it is to be understood that the determina- 18.5° C. or *circ.* 65° F. I find that this tempera- vantages over the temperature 37° C. or 98.4° F., y proposed by me as a suitable standard tempera- y determinations. A temperature of 18.5° C. presents tages: (*a*) coagulation takes place more slowly than ore the determinations can be made more accurately; (*b*) the temperature approximates to the temperature at which ordinary hospital wards are kept; (*c*) the tubes therefore require very little cooling or heating to bring them to the correct temperature; (*d*) the proposed standard temperature is a mean between freezing point and blood heat, and therefore is easily remembered as "half blood heat." [11] *Archiv f. Heilkunde*, 1878. [12] *Vide infra*, effect of alcohol on coagulability. [13] *Proceedings Royal Society*. vol. lv. [14] These statements may, I believe, be accepted as accurate, for they were confirmed by the grandfather, who has an extraordinarily wide experience of hæmophiliac hæmorrhage, as he has stood by the death beds of his six sons who all succumbed to hæmophiliac bleeding or to its sequelæ. [15] The more favourable temperature conditions and the hæmorrhagic increase of coagulability brought about by hæmorrhage that had occurred are no doubt responsible for a good deal of the observed acceleration of coagulation time. It is, however, only legitimate to infer that the administration of calcium chloride was largely contributory to it. [16] Compare the results already recorded of previous additions of lime to the extravascular blood of this child. [17] BRITISH MEDICAL JOURNAL, July 22nd, 1893. [18] Peptone is known to be inefficacious when administered by the stomach. Leech extract has in my experience also proved inefficacious. [19] This hæmorrhage, which had continued for more than a mouth on the regimen of lemon juice, was brought to a complete standstill by the exhibition of 4 grammes of calcium chloride daily diluted in 3 pints of barley water, and taken in sips in order to produce a local as well as a general effect. Coagulation time, which stood at $6\frac{1}{2}$ minutes before the exhibition of lime, came down by gradual steps to $3\frac{3}{4}$ minutes a few days after the commencement of the treatment. [20] *Zeitschrift f. Biologie*, 1882. [21] *Arch. f. Heilkunde*, 1878.